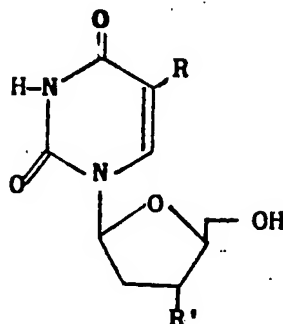




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: <b>PCT/EP91/02134</b> (22) International Filing Date: <b>9 November 1991 (09.11.91)</b> (30) Priority data: 22032 A/90 <b>13 November 1990 (13.11.90) IT</b> (71) Applicants (<i>for all designated States except US</i>): CONSIGLIO NAZIONALE DELLE RICERCHE [IT/IT]; Piazzale Aldo Moro, 7, I-00195 Rome (IT). MENARINI RICERCHE SUD S.P.A. [IT/IT]; Via Tito Speri, 10, I-00040 Pomezia (IT). (72) Inventors; and (75) Inventors/Applicants (<i>for US only</i>): IOTTI, Stefano [IT/IT]; Via E. Torricelli, 23, I-42100 Reggio Emilia (IT). COLONNA, Francesco, Paolo [IT/IT]; Via San Felice, 161, I-40122 Bologna (IT). GARBESI, Anna, Maria [IT/IT]; Via Bonavia, 12, I-40068 San Lazzaro Savena (IT). SPADARI, Silvio [IT/IT]; Via Calabria, 6, I-27100 Pavia (IT). FOCHER, Federico [IT/IT]; Via Don Minzoni, 5, I-27100 Pavia (IT). CIARROCCHI, Giovanni [IT/IT]; Piazza Castello, 8, I-27040 Cigognola (IT). ARCA-MONE, Federico [IT/IT]; Via 4 Novembre, 26, I-20014 Nerviano (IT).</p>		<p>(74) Agent: GERVASI, Gemma; Notarbartolo &amp; Gervasi S.r.l., Viale Bianca Maria, 33, I-20122 Milan (IT). (81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL (European patent), NO, PL, RO, SD, SE (European patent), SN (OAPI patent), SU*, TD (OAPI patent), TG (OAPI patent), US.  <b>Published</b> <i>With international search report.</i></p>

(54) Title: L-2'-DESOXYURIDINES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(I)

(57) Abstract

L-2'-desoxyuridines of formula (I) are described, wherein R = H, CH<sub>2</sub>OC<sub>2</sub>H<sub>5</sub>, CH<sub>2</sub>OH, CH<sub>3</sub>, -CH = CBrH and R' = OH, F, N<sub>3</sub>, and their use for the preparation of pharmaceutical compositions useful for the treatment of viral infections in men and in animals.

# + DESIGNATIONS OF "SU"

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

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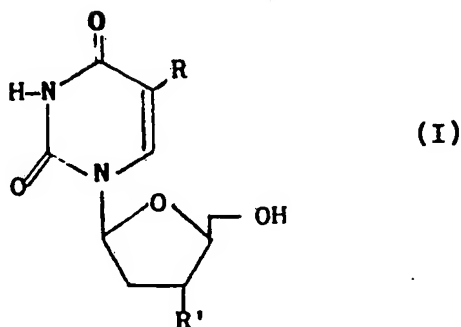
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L-2'-DESOXYURIDINES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM.

Invention field

The present invention relates to L-2'-desoxyuridine of general  
5 formula (I)

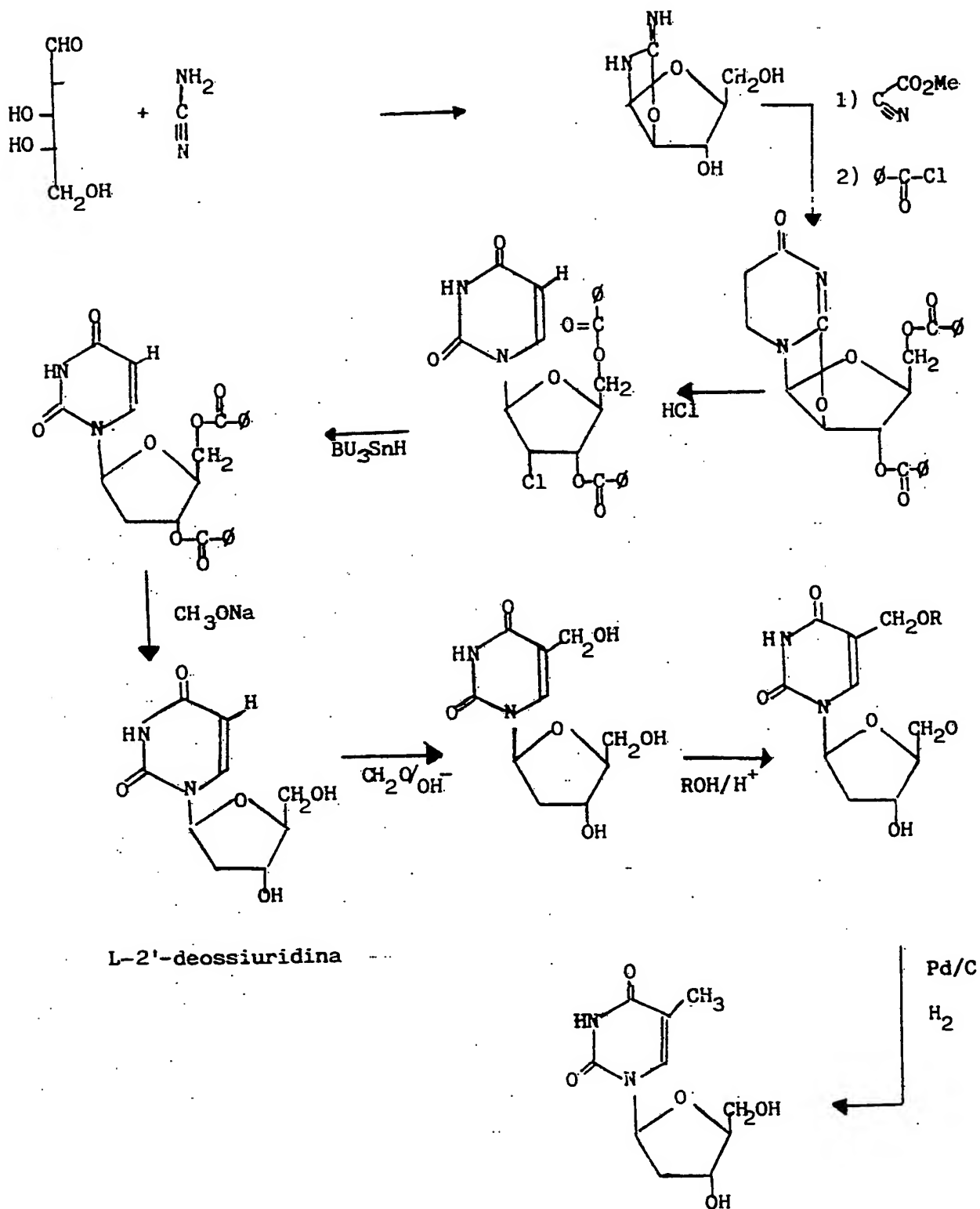
10



wherein R = H, CH<sub>2</sub>OC<sub>2</sub>H<sub>5</sub>, CH<sub>2</sub>OH, CH<sub>3</sub>, -CH=CHBr and R' = OH, F,  
15 N<sub>3</sub> and their use for the preparation of pharmaceutical  
compositions having antiviral properties.

Prior Art

L-2'-desoxynucleosides of formula (I) in which R = H, CH<sub>3</sub>,  
CH<sub>2</sub>OH and R' = OH are known and their synthesis was effected  
20 as described in the literature [Coll. Czech. Chem. Comm. 37, p.  
4072 (1972)] starting from L-arabinose and cyanamid as shown  
hereinbelow, R and R' being as defined supra, H excluded:



It is known furthermore that derivatives of 2'-desoxyuridine belonging to the natural series D are phosphorylated by viral thymidino-kinase [Y.C. Cheng, "Antimetabolites in Biochemistry, Biology and Medicine", Pergamon Press (1979)]. In  
5 "Nucleic Acid Research" 1976, 3 (8), 2143-54 (Eng) is reported that L-uridine, L-cytidine and L-thymidine when administered to mice are largely eliminated in the urine in unmodified form leaving in some tissues only traces of phosphorylated metabolites.

10 In the light of the cited literature, therefore, it was neither known nor could be foreseen that also non-natural 2'-desoxyuridines of the L-series would behave similarly to the natural compounds of the D-series, and even less that they could be employed in the pharmaceutical field.

15 Detailed description of the invention

We have now surprisingly found, and this is an object of the present invention, that compounds of general formula (I) in which  $R = H, CH_2OC_2H_5, CH_2OH, CH_3, -CH=CH_2$  and  $R' = OH, F, N_3$ , are substrates of HSV 1 and HSV 2 thymidino-kinase (that is  
20 they are phosphorylated by the viral enzyme) while they are wholly inert to the action of mammalian thymidino-kinase.

The phosphorylation of these compounds by the viral enzyme is of considerable importance, allowing to obtain drugs capable of inhibiting the development of pathogenous viruses. In fact, in  
25 the infected cell, the analogous monophosphates thus formed

undergo a successive transformation into di-phosphates by the action of the viral thymidino-kinase (TK) and then to triphosphate nucleotides by action of unspecific cellular enzymes. Such analogous triphosphates behave as selective  
5 inhibitors of viral DNA polymerases, or, more frequently, as improved substrates, being preferentially incorporated in the viral DNA destroying its functionality.

In the healthy cell, where, the activation of the non-natural analogous compounds to mono- and di-phosphates does not  
10 take place, neither does their transformation to triphosphates, with a consequent sharp reduction of the toxic effects in the areas not affected by the viral infection.

Particularly the present invention relates to pharmaceutical compositions having antiviral properties containing as active  
15 principle an L-2'-desoxyuridine of general formula (I), wherein  $R = H, CH_2OC_2H_5, CH_2OH, CH_3, -CH=CBrH$  and  $R' = OH, F, N_3$  and a pharmaceutically acceptable excipient or vehicle. The compounds of formula (I) wherein  $R = -CH=CBrH, CH_3$ , and  $R' = OH, F, N_3$ , with the proviso that when  $R = CH_3$ ,  $R'$  is not OH,  
20 are new.

According to the present invention, the preferred compounds of general formula (I) suitable for the above said purposes are:

- 1-(2-desoxy- $\beta$ -L-erythro-pentafuranosyl)-2,4-(1H,3H)  
pyrimidindione ( $R = H, R' = OH$ )
- 25 - 1-(2-desoxy- $\beta$ -L-erythro-pentafuranosyl)-5-hydroxymethylen-  
2,4-(1H,3H)-pyrimidindione ( $R = CH_2OH, R' = OH$ )

- 1-(2-desoxy- $\beta$ -L-erythro-pentafuranosyl)-5-ethoxymethylen-  
2,4-(1H,3H)-pyrimidindione ( $R = CH_2OC_2H_5$ ,  $R' = OH$ )
- 1-(2-desoxy- $\beta$ -L-erithro-pentafuranosyl)-5-methyl-2,4-  
(1H,3H)-pyrimidindione ( $R = CH_3$ ,  $R' = OH$ )
- 5 - 1-(2-desoxy- $\beta$ -L-erythro-pentafuranosyl)-5-(E-2-bromovinyl)-  
2,4-(1H,3H)-pyrimidindione ( $R = -CH=CHBr$ ,  $R' = OH$ )
- 1-(2,3-didesoxy-3-azido- $\beta$ -L-erythro-pentafuranosyl)-5-  
methyl-2,4-(1H,3H)-pyrimidindione ( $R = CH_3$ ,  $R' = N_3$ )
- 1-(2,3-didesoxy-3-fluoro- $\beta$ -L-erythro-pentafuranosyl)-5-  
10 methyl-2,4-(1H,3H)-pyrimidindione ( $R = CH_3$ ,  $R' = F$ )

The first four compounds were described in the literature without, however, any reference to their antiviral properties and their ensuing pharmaceutical use, while the others are new. For illustrative, non limiting, purposes, we are now reporting  
15 the preparation of one compound according to the present invention.

#### EXAMPLE 1

Synthesis of 1-(2-desoxy- $\beta$ -L-erythro-pentafuranosyl)-5-methyl-  
2,4(1H,3H)-pyrimidindione ( $R = CH_3$ ,  $R' = OH$ ).

- 20 A mixture of 4.6 g L-2'-desoxyuridine (compound of formula (I) in which  $R = H$ ,  $R' = OH$ ), 20 ml 1 M KOH and 20 ml aqueous 37% formaldehyde is kept at 60°C for five days, adding every 24 hours 5 ml 1 M KOH and 5 ml aqueous 37% formaldehyde. The reaction mixture is then diluted with an equal volume of water,  
25 the pH is brought to 3 by addition of Dowex 50 ( $H^+$ ) ion

exchange resin, then filtered washing the resin with 200 ml water; filtrate and washing water are put together and evaporated under reduced pressure. The residue is then co-evaporated for three times with absolute ethanol, dissolved in 5 50 ml of same solvent, made alkaline by addition of triethylamine, evaporated under reduced pressure and dried by co-evaporation with 50 ml toluene (twice). The residue is kept for one night under reduced pressure over phosphoric anhydride, then 200 ml absolute ethanol are added and the solution 10 obtained is brought to pH 2.5 by addition of concentrated hydrochloric acid and heated on reflux for 2 hrs.

After cooling, the reaction mixture is made alkaline by addition of triethylamine and evaporated; the residue is chromatographed on silica gel eluting with a methylene 15 chloride/methanol 85ml/15ml mixture.

The obtained compound is then dissolved in 200 ml absolute ethanol, 0.5 ml concentrated hydrochloric acid and 1 g palladium 10% on carbon are added, followed by hydrogenation at normal pressure for 3 hrs. The reaction mixture is filtered on 20 Celite, which is washed with 100 ml ethanol. The filtrate are put together, made alkaline with triethylamine and evaporated under reduced pressure. The residue is crystallized from 8 ml absolute ethanol.

Thus 2 g L-thymidine  $[\alpha]_D^{20} = -18.5^\circ$  (c = 1% in water).

25 With a method similar to the one described in the literature for the compounds derived from D-2'-desoxyuridine, and



employing the suitable reagents, one can obtain also the other previously indicated compounds of formula (I).

#### Biological activity

The biological activity of the compounds according to the present invention in the treatment of viral infections was evaluated employing HSV 1 TK and cell TK.

Fig. 1 shows the L-thymidine effect on the enzymatic activities of Herpes simplex 1 virus TK and of the human one.

Fig. 1 shows that L-thymidine inhibits the phosphorylation of (D)-thymidine by Herpes simplex 1 TK ( $\square$ ), but not by human TK ( $\blacklozenge$ ).

The test consists in measuring the amount of (D)-thymidine substrate phosphorylated to (D)-TMP (ordinates) in the presence of growing L-thymidine concentrations (abscissae). The viral or cellular purified enzyme (0.07 units) was incubated for 15 minutes at 37°C in 25  $\mu$ l of a mixture containing 30 mM Hepes-K, pH 7.5, 6 mM  $\text{MgCl}_2$ , 6 mM ATP, 0.5 mM dithiothreitol (DTT), 10  $\mu$ M [ $^3\text{H}$ ]Thy (25 Ci/mmol) and various L-thymidine concentrations.

The reaction is stopped depositing 20  $\mu$ l of the mixture on DE-81 filters which are immediately soaked in an excess of 1 mM ammonium formate, pH 5.6, in order to eliminate the (D)-[ $^3\text{H}$ ]thymidine not transformed into monophosphate and which cannot therefore bind itself with the positive charges of the DE-81 filter.

The filters are then washed in distilled water for 5 minutes and dehydrated in ethyl alcohol for 5 minutes. The radioactive D-TMP bound to the filter was evaluated in a  $\beta$  radiation counter.

- 5 One can clearly observe a specific inhibition of viral TK; in fact at 5  $\mu\text{g/ml}$  viral TK is 90% inhibited, whereas the human one is completely resistant. Human TK proved to be fully resistant to L-thymidine even at the highest investigated dose (200  $\mu\text{g/ml}$ ).
- 10 L-thymidine competes with D-thymidine for the active site of the viral enzyme, as proved by the competitive type inhibition curves reported in Fig. 2, which is a representation according to Lineweaver-Burk of the effect of L-thymidine on the TK activity of Herpes simplex virus in the presence of different
- 15 concentrations of D- $^3\text{H}$  thymidine substrate (expressed in the abscissae as the inverse of concentration).

The viral enzyme (0.07 units) was incubated for 15 minutes at 37°C in 25  $\mu\text{l}$  of a mixture containing 30 mM Hepes-K, pH 7.5, 6 mM  $\text{MgCl}_2$ , 6 mM ATP, 0.5 mM dithiothreitol (DTT), various

20 concentrations of D- $^3\text{H}$ thymidine(25 Ci/mmol) and various concentrations of L-thimidine (0  $\mu\text{M}$  [□], 2  $\mu\text{M}$  [◆], 5  $\mu\text{M}$  [■], 10  $\mu\text{M}$  [◇], 15 mM [■]). The reaction is stopped by depositing 20  $\mu\text{l}$  of the mixture on DE-81 filters which are processed as indicated in Fig. 1. The D-TMP values are reported as the

25 inverse of the concentration on the ordinates. From the experiment one concludes that  $K_m$  for D-thymidine viral enzyme

is 2.8  $\mu\text{M}$  and that  $K_i$  for L-thymidine is 2  $\mu\text{M}$ .

To check whether L-thymidine is phosphorylated by the viral enzyme, as happens for D-thymidine, IDU, TFT, ACU etc., or whether it simply inhibits the synthesis of the natural  
5 substrate competing for the active site, as it happens for the other compounds which we have studied, such as phenyl-desoxyguanosine (Ph-dG) we have analysed by HPLC the products of the reaction catalyzed by viral TK, between [ $\gamma$ - $^{32}\text{P}$ ] ATP and L-thymidine.

- 10 The investigated nucleosides and nucleotides were separated by the reverse-phase method employing the Bio-Rad 100 MAPS preparative system.

A reverse-phase  $\text{C}_{18}$  Bio Sil ODS-5S (0.4 x 15 cm) column was employed under the following conditions: injected volume 20  $\mu\text{l}$ ;  
15 UV : 260 nm; temperature : room; eluent : buffer A (20 mM  $\text{KH}_2\text{PO}_4$ , pH 5.6), buffer B (20 mM  $\text{KH}_2\text{PO}_4$ , pH 5.6, 60% methanol). The specific conditions for separating L-thiomidine ATP are as follows: from 0 to 20 min. a 0% to 70% buffer B gradient; from 20 to 30 min. a 70% to 77% buffer B gradient and from 30 to 32  
20 min. a 77% to 100% buffer B gradient. Flux was 0.5 ml/min. The enzymatic reaction (0.3 units viral enzyme) was performed as previously described, except that, instead of 6 mM ATP, 100  $\mu\text{M}$  [ $\gamma$ - $^{32}\text{P}$ ] ATP 1500 cpm/pmol was employed and that the 37°C incubation was protracted to 30 min. The results obtained are  
25 reported in Fig. 3, in which on the abscissae of each panel A,

B and C the number of fractions eluted by the column is reported. In each fraction, the radioactivity was determined, which is reported as counts per minute (cpm) on the respective ordinates.

5 Panel A shows the control data without Thy, panel B the data for 10  $\mu$ M L-thymidine and panel C the data for 10  $\mu$ M D-thymidine in the assay.

As can be seen from Fig. 3, viral TK phosphorylates L-thymidine: in fact, in the presence of L-thymidine a  
10 radioactivity peak in the same position as D-TMP (Panel C) is obtained.

In the 30 min. reaction, viral TK phosphorylates 70% of the L-thymidine present in the assay, which is comparable to what is obtained with natural D-thymidine.

#### 15 Pharmaceutical Compositions

The pharmaceutical compositions according to the present invention comprise, as an active component, a therapeutically effective amount of a L-desoxyuridine of general formula (I) in which R and R' have the previously indicated meanings, or one  
20 of its pharmaceutically acceptable salts, in association with one or more pharmaceutically acceptable excipients or vehicles.

The pharmaceutical compositions according to the invention may be administered per os, parenterally and topically in suitable pharmaceutical formulations, for instance as sterile solutions  
25 for injectable use, tablets, capsules, powders, granulates, syrups, collyria, ointments, creams, suppositories, ovules,

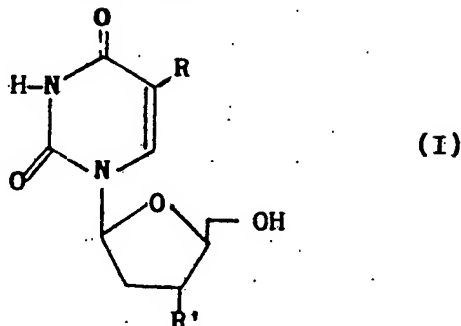
bougies, etc.

The active principle is contained in the pharmaceutical compositions according to the invention in amounts variable between 50 mg and 2 g per dose, depending on the way of  
5 administration.

Useful excipients in the formulations according to the invention are e.g. jellying agents, auxiliaries for gelatine capsules, antioxidants, dispersing agents, emulsifiers, anti-foam agents, taste correcting agents, preservers, solubilyzing  
10 agents, etc.

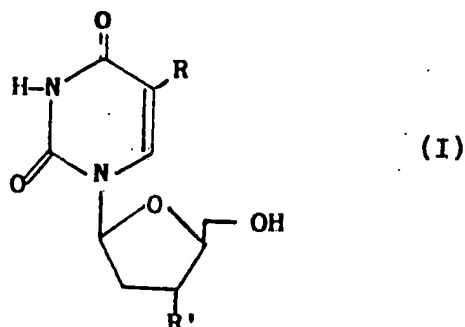
## CLAIMS

- 1 1. L-2'-desoxyuridines of general formula (I)



- 2 wherein R =  $-\text{CH}=\text{CBrH}$ ,  $\text{CH}_3$  and  $\text{R}' = \text{OH}$ , F,  $\text{N}_3$ , with the proviso  
 3 that when R =  $\text{CH}_3$ ,  $\text{R}'$  is not OH, and their pharmaceutically  
 4 acceptable salts.
- 1 2. Compound of general formula (I) according to claim 1,  
 2 wherein R =  $-\text{CH}=\text{CBrH}$  and  $\text{R}' = \text{OH}$  and its pharmaceutically  
 3 acceptable salts.
- 1 3. Compound of general formula (I) according to claim 1,  
 2 wherein R =  $\text{CH}_3$  and  $\text{R}' = \text{N}_3$  and its pharmaceutically acceptable  
 3 salts.
- 1 4. Compound of general formula (I) according to claim 1,  
 2 wherein R =  $\text{CH}_3$  and  $\text{R}' = \text{F}$  and its pharmaceutically acceptable  
 3 salts.
- 1 5. Pharmaceutical compositions containing as active principle  
 2 an effective amount of a compound according to claim 1 and  
 3 pharmaceutically acceptable excipients or vehicles.
- 1 6. Pharmaceutical composition according to claim 5 wherein the  
 2 active principle is a compound of formula (I) wherein R =  
 3  $-\text{CH}=\text{CBrH}$  and  $\text{R}' = \text{OH}$  and its pharmaceutically acceptable salts.

- 1 7. Pharmaceutical composition according to claim 5 wherein the  
2 active principle is a compound of formula (I) wherein  $R = CH_3$   
3 and  $R' = N_3$  and its pharmaceutically acceptable salts.
- 1 8. Pharmaceutical composition according to claim 5 wherein the  
2 active principle is a compound of formula (I) wherein  $R = CH_3$   
3 and  $R' = F$  and its pharmaceutically acceptable salts.
- 1 9. Pharmaceutical compositions according to claim 5 having  
2 antiviral activity.
- 1 10. Pharmaceutical compositions according to claim 5 for the  
2 therapeutic treatment of Herpes simplex.
- 1 11. Pharmaceuticals compositions containing as active  
2 principle an effective amount of a compound of formula (I)



- 3 wherein  $R = H, CH_2OC_2H_5, CH_2OH$  and  $R' = OH, F, N_3$  or  $R = CH_3$   
4 and  $R' = OH$  and their pharmaceutically acceptable salts and  
5 pharmaceutically acceptable excipients or vehicles.
- 1 12. Pharmaceutical composition according to claim 11 wherein  
2 the active principle is a compound of formula (I)  
3 wherein  $R = H$  and  $R' = OH$  and its pharmaceutically acceptable  
4 salts.
- 1 13. Pharmaceutical composition according to claim 11 wherein

2 the active principle is a compound of formula (I) wherein R =  
3 CH<sub>2</sub>OH and R' = OH and its pharmaceutically acceptable salts.

1 14. Pharmaceutical composition according to claim 11 wherein  
2 the active principle is a compound of formula (I)  
3 wherein R = CH<sub>2</sub>OC<sub>2</sub>H<sub>5</sub> and R' = OH and its pharmaceutically  
4 acceptable salts.

1 15. Pharmaceutical composition according to claim 11 wherein  
2 the active principle is a compound of formula (I) wherein R =  
3 CH<sub>3</sub> and R' = OH and its pharmaceutically acceptable salts.

1 16. Pharmaceutical compositions according to claim 11 having  
2 antiviral activity.

1 17. Pharmaceutical compositions according to claim 11 for the  
2 therapeutic treatment of Herpes simplex

1 18. Pharmaceutical compositions according to claims 5 or 11  
2 wherein the active principle is contained in an amount of  
3 between 50 mg and 2 g.

1 19. Pharmaceutical compositions according to claims 5 or 11,  
2 for parenteral, oral or topical administration.

1 20. Pharmaceutical compositions according to claims 5 or 11 in  
2 the form of injectable sterile solutions, tablets, capsules,  
3 granulates, powders, syrups, collyria, ointments, creams,  
4 suppositories, ovules, bougies.



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FIG. 1

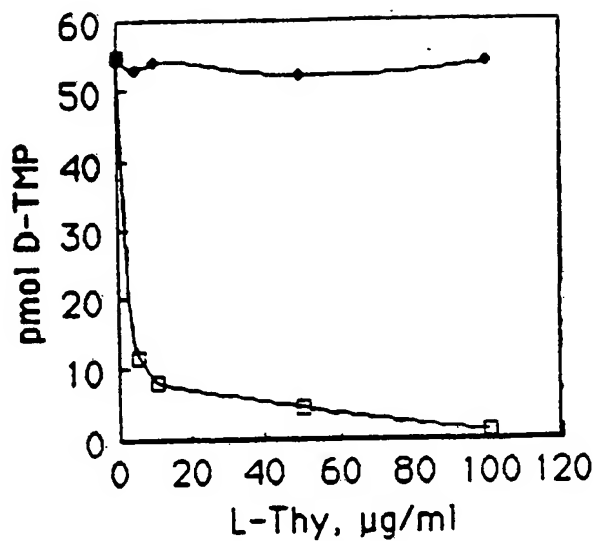


FIG. 2

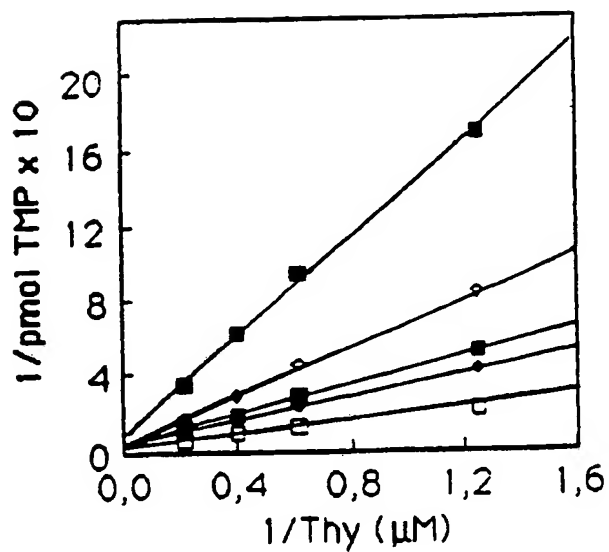
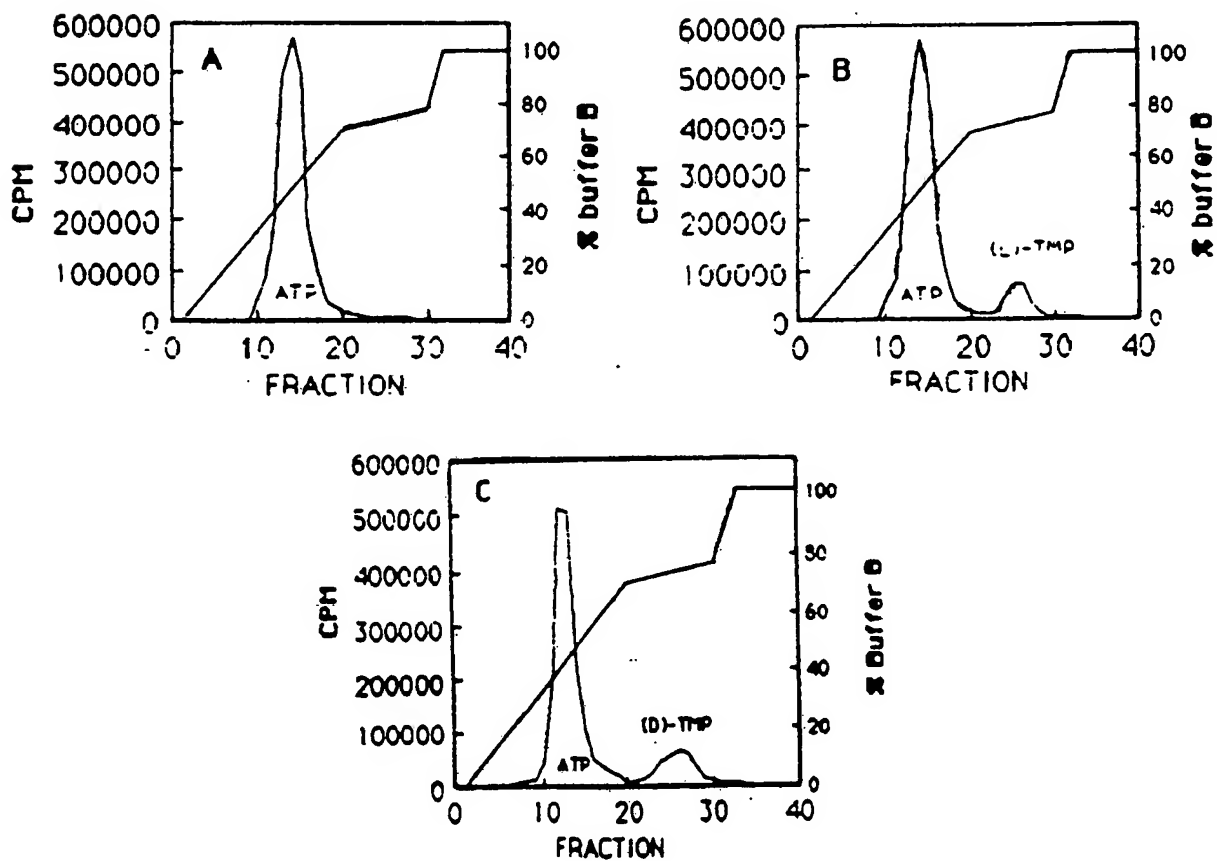


FIG. 3



**I. CLASSIFICATION OF SUBJECT MATTER** (If several classification symbols apply, indicate all)<sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07H19/073; A61K31/70

**II. FIELDS SEARCHED**Minimum Documentation Searched<sup>7</sup>

Classification System	Classification Symbols
Int.Cl. 5	C07H ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched<sup>8</sup>**III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>**

Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	EP,A,0 352 248 (MEDIVIR AKTIEBOLAG) 24 January 1990  see the whole document ---	1,3-5, 7-12, 15-20
Y	FR,A,2 627 492 (INSTITUT DE RECHERCHES CHIMIQUES ET BIOLOGIQUES APPLIQUEES) 25 August 1989  see abstract ---	1,3-5, 7-12, 15-20
Y	WO,A,8 906 655 (UNIVERSITE PIERRE ET MARIE CURIE) 27 July 1989  see abstract ---	1,3-5, 7-12, 15-20
Y	EP,A,0 217 580 (THE WELLCOME FOUNDATION LTD.) 8 April 1987  see claims 4,11 ---	1,3-5, 7-12, 15-20
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

**IV. CERTIFICATION**

Date of the Actual Completion of the International Search

16 JANUARY 1992

Date of Mailing of this International Search Report

13.02.92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

SCOTT J.R.

J.R.M. Scott 26171

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	EP,A,O 254 268 (AKADEMIE DER WISSENSCHAFTEN DER DDR) 27 January 1988  see abstract	1,3-5, 7-12, 15-20
A	COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS. vol. 37, no. 12, December 1972, PRAGUE CS pages 4072 - 4087; A.HOLY: 'Nucleic Acid Components and their Analogues. CLIII. Preparation of 2'-deoxy - L - Ribonucleosides of the Pyrimidine Series.' cited in the application see abstract see page 4073, compound VII see page 4075, compounds XX, XXI, XXII	1,3-5, 7-12, 15-20
X,P	JOURNAL OF ORGANIC CHEMISTRY. vol. 56, no. 11, 24 May 1991, EASTON US pages 3591 - 3594; J.WENGEL ET AL.: 'Synthesis of L-3'-Azido-3'-deoxythymidine and its Stereoisomers' see the whole document	1,3,5,7, 9-11,16, 18-20

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

EP 9102134  
SA 52789

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on  
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